Lasting impact of lipid nanoparticles

Lipid nanoparticles are going into billions of arms in the form of COVID-19 mRNA vaccines, delivering, at last, on the promise of nanotechnology to revolutionize drug delivery. Revolutions have the ability to alter the course of history. In the case of nanotech-based drug delivery, with many promising applications being explored, it looks like lipid nanoparticles have done just that.

Almost exactly 1 year ago, UK regulators granted emergency-use authorization to the COVID-19 mRNA vaccine developed by Pfizer and BioNTech, followed by approval of Moderna's mRNA vaccine. In many ways, this was a historic moment. Not only were these vaccines the first mRNA vaccines authorized for clinical use, they were also developed within only 3 months of sequencing the viral genome of SARS-CoV-2 and showed an astonishing efficacy of >90% in preventing COVID-19 disease. Without doubt, the approval of the COVID-19 mRNA vaccines also marked a milestone in nanotechnology. Without lipid nanoparticles, COVID-19 mRNA vaccines would not exist.

The clinical success of COVID-19 mRNA vaccines is built on many years of fundamental and clinical research, from the design of tools to produce biologically active mRNA to the transformation of mRNA into a drug platform. Importantly, the lipid nanoparticles required for mRNA delivery had to be engineered and optimized to ultimately enable safe and efficient mRNA vaccines. This was by no means an easy task. The groundwork for lipid-based drug delivery systems was laid more than 40 years ago in the lab of Pieter Cullis. We talked to Pieter about how his basic research on lipid asymmetry provided the foundations for the encapsulation of nucleic acids into lipid systems. The story of lipid nanoparticles perfectly exemplifies the importance of fundamental science in nanomedicine; without a thorough understanding of lipid and nanoparticle behaviour, mRNA delivery would not have been possible. Yet, to get technologies out of the lab and into the clinic, greater resources and collaborations across fields are needed, beyond the academic system.

The beauty of lipid nanoparticles is that they can serve as a platform technology, in which the same nanoparticle is able to deliver a variety of nucleic acids. As Pieter puts it: "Once you know the protein you wish to silence or express, the requisite siRNA or mRNA can be synthesized in a month or two, and can be packaged in a lipid nanoparticle in a day or two to provide a targeted drug." Indeed, several lipid nanoparticle–mRNA vaccines against other infectious diseases, various cancers and genetic disorders are already in clinical trials or clinical studies, as discussed in a Review in this issue by Yizhou Dong, Tal Zaks, Robert Langer and colleagues, and new mRNA flu vaccines have just entered clinical trials. The composition and chemistry of lipid nanoparticles can further be tailored to target specific tissues, and researchers have already engineered designs that allow delivery of mRNA directly into the lungs by inhalation. The community is also working on improving large-scale manufacturing and temperature stability of lipid nanoparticles to address problems associated with cold chain requirements and distribution. After all, vaccines don't save lives — vaccinations do.

Although lipid nanoparticles have now finally gotten the deserved attention, other nanoparticles are also promising candidates for various clinical applications. In a Comment in this issue, Chengzhong Yu, Amirali Popat and colleagues highlight clinical trials of silica nanoparticles — inorganic nanoparticles that offer high drug loading capacity, good mechanical stability and the possibility to release drugs in response to internal or external stimuli. Silica nanoparticles are, for example, being investigated for localized cancer therapy and as imaging agents, with several clinical trials already completed.

Nanoparticles can also be made of synthetic polymers, peptides, proteins or nucleic acids, and the drug delivery community has an eye on extracellular vesicles, which are naturally occurring, complex nanoparticles with the inherent ability to safely transport biomolecules throughout the body. However, the more complex the nanoparticle, the more difficult it may be to achieve regulatory approval. In fact, all clinically approved nanomedicines are based on simple designs encompassing only a small number of components. That said, there was a time in nanomedicine when lipid nanoparticle-based drug delivery was also deemed too complex to ever find widespread application in humans, and many questioned its clinical impact and commercialization potential. Well, they were proven wrong.

mRNA vaccines may not have received the Nobel Prize this year, but their clinical success will have a lasting impact beyond COVID-19. Clearly, lipid nanoparticles are on a roll, and the nanomedicine community will certainly capitalize on their clinical success. There are plenty of applications beyond vaccines to explore and nanoparticle designs to be improved. Maybe there are even better ways to deliver drugs into cells? The nanotech future will tell. The revolution has only just begun.